

The oral allergy syndrome: improved diagnostic and treatment methods

Adriano Mari^a, Barbara K. Ballmer-Weber^b and Stefan Vieths^c

Purpose of review

The aim of this article is to review recent clinical and molecular findings related to the oral allergy syndrome in order to define its relevance in the field of food allergy, describe current diagnostic approaches and discuss attempts to use specific immunotherapy for treatment.

Recent findings

New allergenic sources causing the oral allergy syndrome have been reported. Their allergenic molecules have been identified. In most of those studies oral allergy syndrome is reported as a clinical manifestation among more severe ones. Some of the molecules generally considered not to be at risk for severe reactions have been demonstrated to pose a threat for inducing generalized reactions. Some studies tried to assess the usefulness of immunotherapy with birch pollen extract by either subcutaneous or sublingual routes for the treatment of associated food allergies. In most of the cases, a well defined study design and a molecular approach at different study levels are lacking and thus the value of the obtained results is limited. To date, no final conclusion can be drawn on the basis of reported results.

Summary

The knowledge about the highly prevalent phenomenon of oral allergy syndrome is still incomplete, in respect to both, epidemiology and foods inducing symptoms. It is very important to reach consensus on several aspects of this food-induced allergic disease. Further studies are required to highlight whether immunotherapy using co-recognized inhalant allergens is an effective way of curative treatment, or if co-treatment with purified pollen-related food allergens will be required to obtain a long-lasting effect.

Keywords

allergen, co-recognition, cross-reactivity, food allergy, oral allergy syndrome, specific immunotherapy

Abbreviations

DBPCFC	double-blind placebo-controlled food challenge
LTP	lipid transfer protein
OAS	oral allergy syndrome
SCIT	specific subcutaneous immunotherapy
SLIT	specific sublingual immunotherapy

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Introduction

The term 'oral allergy syndrome' (OAS) defines a complex of symptoms induced by exposure of the oral and pharyngeal mucosa to food allergens. Affected subjects may report symptoms of increasing severity, from mild itching of the lips, mouth and throat, to lip and tongue swelling, to severe angioedema of the pharyngeal mucosa up to life-threatening emergencies [1].

The OAS is the most common food allergy-related manifestation and can be present either isolated or in association with systemic cutaneous or respiratory symptoms, and may even result in anaphylaxis [1–4]. OAS may be the first manifestation of food allergy in the natural course of the disease toward more severe reactions [3]. OAS is generally thought to be related to plant-derived foods only [3], but also severe reactions to animal-derived foods may be preceded and accompanied by local oral symptoms [5]. In view of more severe manifestations, induced for instance by animal derived foods, underreporting of initial oral mucosa symptoms has to be taken into consideration. The awareness of OAS as an important alarm manifestation may contribute to a timely therapeutic intervention in subjects at risk for severe food-induced allergic symptoms.

The OAS can be considered a worldwide problem, related or not to pollen sensitization [3,6–9]. The triggering food may be dependent on geographically different nutritional habits and may thus vary from place to place [3]. The local pattern of foods causing OAS may change when new foods start to be consumed outside the native area [10•].

In contrast to food-dependent allergic reactions induced by gastric or intestinal absorption, where digestion may affect allergen structure, OAS is most likely induced by exposure to native non-modified allergens. As a consequence, even unstable or rapidly degradable allergens are

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^aAllergy Unit, National Health Service, Rome, Italy, ^bAllergy Unit, Department of Dermatology, University Hospital Zurich, Zurich, Switzerland and ^cDepartment of Allergology, Paul-Ehrlich-Institut, Langen, Germany

Correspondence to: Adriano Mari, MD, Via Malipiero 28, 04100 Latina, Italy
Tel: +39 330860005; fax: +39 0773 620787; e-mail: a.mari@panservice.it

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able to cause OAS. From this point of view, the exposure through the oral mucosa has much more similarity to the exposure via the respiratory mucosa rather than exposure through the gut mucosa. The clinical manifestation of OAS and the degree of related symptoms are highly influenced by chemical/physical pre-ingestion manipulation of the food (storage, preservation, freezing, peeling, cooking) [11,12^{*},13^{*}]. Although protein absorption through oral mucosa, including allergens, has not been as extensively studied as absorption through the gastrointestinal mucosa [14], it can be assumed that oral absorption happens in the same way as shown for allergens contained in extract preparations for sublingual specific immunotherapy (SLIT) [15]. The known fact, that food allergy may be triggered by kissing, may be taken as further evidence that allergen penetration through the oral mucosa does happen [16,17].

Allergenic sources and molecules causing oral allergy syndrome

New food sources causing OAS or a better molecular characterization of previously identified allergenic food proteins have been recently reported in numerous papers. Allergen names reported in the present article are taken from the official World Health Organization/International Union of Immunological Societies allergen nomenclature website (as of 22 November 2004 release). If not available from that source, names given by authors or available in other allergen web sites (Table 1) are used.

Tabar and colleagues [18^{*}] examined a group of 27 patients reporting uncommon allergy symptoms on exposure to asparagus. One patient reported isolated OAS caused by asparagus ingestion. This person had a positive skin test to a lipid transfer protein (LTP) purified from fresh asparagus (Aspa o 1).

Willeroider and co-workers [19] studied 34 patients with allergy symptoms caused by bell pepper. Thirteen (38%) reported OAS. In three patients OAS was the unique

reported symptom, whereas in the remaining participants OAS was associated with rhinitis, asthma, urticaria, and atopic dermatitis. Profilin was identified as the causative molecule and denominated as Cap a 2, sharing high amino acid sequence identity with other pollen and food profilins, and being cross-reactive with tomato profilin (Lyc e 1).

Scheurer *et al.* [20^{*}] characterized Pru av 3, the LTP from cherry. Fourteen subjects with Pru av 3 sensitization suffered from OAS, which was associated in some of the patients with gastrointestinal, respiratory or cardiovascular symptoms. Thermal processing and protease treatment of Pru av 3 did not influence its IgE binding capacity, suggesting stability as one of the main features for LTP allergenicity.

Cadot *et al.* [21] reported on four subjects with OAS due to non-occupationally acquired chicory sensitization. He demonstrated that although those patients were sensitized to birch pollen and Bet v 1, other allergens could be the cause of their symptoms.

Allergy to fig fruit has been reported in two papers [22,23] and in addition as part of an extensive survey on food hypersensitivity [7]. Two subjects described by Antico *et al.* [22] showed fig-induced OAS associated with respiratory symptoms. A partial characterization of allergenic proteins derived from different parts of the fig fruit was carried out by immunoblotting. An extensive characterization of the IgE reactivity to fig allergens was performed by Focke and co-workers [23] studying five fig allergic subjects. Reactivity to fresh and dried figs was described by the authors to be related to *Ficus benjamina* exposure and sensitization. Indirect evidence of IgE to ficin from fig fruit resulted from testing the homologous cysteine protease papain from papaya (Car p 3). Positive tests were found in three of five subjects.

Two recent surveys confirmed hazelnuts as an important cause of food allergy, including OAS [4,7]. Reactivity to unprocessed and processed (roasted) hazelnuts has been assessed by in-vivo and in-vitro methods [11]. IgE reactivity to Cor a 1.04 (Bet v 1-homologous) and Cor a 2 (profilin) was detected. Double-blind placebo-controlled food challenge (DBPCFC) showed that the majority of individuals with allergy to raw hazelnut were not more reactive to processed hazelnuts. Five patients, however, still reacted to hazelnuts after thermal treatment, suggesting that traces of pollen-related allergens remained active in the roasted nuts used. This means that tolerance to processed foods has to be evaluated individually in patients even if they are sensitized to labile pollen-related allergens. A second study [24^{*}] described Cor a 8, the LTP allergen in hazelnut, as causing food-induced allergic diseases, including OAS and more severe

Table 1. Allergenic molecule databases available from the Internet

Website	URL
WHO/IUIS ^a	http://www.allergen.org/
ALLERGEN Database	http://research.i2r.a-star.edu.sg/Templar/DB/Allergen/
Allergome	http://www.allergome.org/
The Biotechnology Information for Food Safety Database	http://www.iit.edu/~sgendel/fa.htm
The Allergen Database: ADB	http://allergen.csl.gov.uk/
Farrp Allergen Database	http://www.allergenonline.com/
Informall Database	http://foodallergens.ifr.ac.uk/
SDAP: Structural Database of Allergenic Proteins	http://fermi.utmb.edu/SDAP/

^aOfficial web site of the World Health Organization/International Union of Immunological Societies (WHO/IUIS) allergen nomenclature sub-committee.

symptoms in the majority of patients. Recombinant Cor a 8 was found to be a useful diagnostic tool to identify hazelnut-sensitized patients.

Two patients showing OAS to jackfruit followed by systemic symptoms, confirmed by a DBPCFC, were described by Bolhaar and colleagues [10^{••}]. A new 17 kD Bet v 1-homologue was detected (Art i 17kD) and suggested as one of the possible triggering allergens. In the reported cases allergy to jackfruit seemed to be secondarily acquired after a previously established sensitization to Bet v 1. As shown for jackfruit, introduction of non-local food from different geographical areas may lead to the identification of new allergenic foods.

Allergy symptoms caused by kiwi fruit were reported in three surveys [3,4,7]. Four studies focused specifically on green kiwi allergy [13[•],25[•],26[•],27^{••}]. Lucas *et al.* [25[•]] reported that 65% of 276 subjects with self-diagnosed kiwi allergy had OAS, which was in many cases associated with systemic symptoms. After a DBPCFC class I food allergy to kiwi was confirmed in 24 of 45 tested subjects. In-vivo and in-vitro comparative evaluation has been carried out using commercial extracts and fresh fruits for skin tests, and enzyme immunoassay and immunoblotting for IgE detection. Aleman *et al.* [26[•]] used DBPCFC to confirm kiwi allergy diagnosis in 33 patients. They identified several subgroups of kiwi allergic patients. Most of these participants reported OAS either isolated or associated with systemic symptoms. The IgE immunoblot testing of sera did not show a specific pattern of reactivity when compared with clinical pictures. Several allergens were recognized by IgE of allergic patients including the already known Act c 1 (actinidin) and Act c 2, a thaumatin-like protein (TLP). Fiocchi and co-workers [13[•]] described the thermal lability of kiwi allergens. They used sera from children tested DBPCFC positive to kiwi fruit and reacting with an OAS. This finding suggests that kiwi products that are industrially processed by heat treatment may be safely consumed by pediatric kiwi allergic subjects. Bublin and colleagues [27^{••}] studied IgE reactivity to green kiwi of participants from three European countries (Austria, Italy, The Netherlands), most of them having OAS and associated systemic symptoms. They found differences between allergens recognized by sera from northern European countries and those available from Italian patients. Actinidin (Act c 1) was recognized by IgE from almost all the Northern European patients, but by less than 50% of the Italian patients. Furthermore, the authors identified and characterized four allergenic molecules from green kiwi fruit (Act c 1, Act c 2, a chitinase and a phytocystatin). In the same paper the first detailed study of gold kiwi fruit allergens has been carried out. Homologous chitinase, TLP, and phytocystatin allergens were described, whereas an actinidin-like protein seemed not to be

expressed in gold kiwi fruit. If this finding will be confirmed, it could imply the possibility that gold kiwi fruit may be tolerated by patients exclusively sensitised to Act c 1. Moreover, the authors suggested a different allergen nomenclature on the basis of the updated taxonomic kiwi plant identification.

Fourteen patients with food allergy to lettuce were studied by Miguel-Moncin and colleagues [28]. OAS was followed by more severe symptoms in the majority of cases. The authors identified LTP (Lac s 1) as the responsible allergen.

Melon allergy causing OAS has been reported in two papers [29,30]. Profilin (Cuc m 2) was identified as the causative allergen in 71% of 21 subjects. IgE binding to Cuc m 2 was demonstrated to be unaffected by human saliva but quickly digested by simulated gastric fluid [30].

Mittag and co-workers [31^{••}] reported 20 Swiss and Dutch patients with peanut-related symptoms. All patients had OAS, and 60% of them had one or more additional systemic symptom. Both local and systemic manifestations were reproduced during DBPCFC. A new peanut allergen (Ara h 8) was identified as a Bet v 1-related molecule, characterized, and cloned. Ara h 8 was found to be labile upon heating and pepsin digestion completely removed its IgE reactivity. These findings suggested that systemic symptoms in the studied patients possibly occurred because of oral mucosa absorption of intact allergen.

Similarly to Ara h 8, the same research group [32^{••}] described patients with associated birch pollen and soy allergy. Symptoms caused by different soy-based commercial products ranged from OAS to anaphylaxis. Gly m 4, a previously identified and cloned Bet v 1-related soy allergen [32^{••},33], was the relevant molecule causing soy-related symptoms. Gly m 4 concentration during soy ripening and storage was studied. Final products undergoing different food processing procedures showed a variable concentration of the allergen. The authors estimated that 10% of birch pollen allergic patients may have soy-related symptoms.

An interesting review on spices inducing allergy was published by Schöll and Jensen-Jarolim [34[•]]. The authors, giving a full description of all the spice-induced allergic manifestations, reported Bet v 1 and profilin-related molecules as allergens in anise (Pim a 1 and 2), cumin (Cum c 1 and 2), fennel (Foe v 1 and 2), celery (Api g 1 and 4), coriander (Cor s 1 and 2), and parsley (Pet c 1 and 2). Furthermore, several other allergens belonging to other functional groups were reported to exist in spices (LTP, 2S albumins, osmotin-like, vicilins).

Tomato-induced OAS has been reported in 33 of 50 patients with tomato allergy [35[•]]. Lyc e 1, tomato profilin, was identified as the causative allergen, and its biochemical and immunochemical relationships with other profilins was studied [19,35[•]]. In another study, a second tomato allergen Lyc e 2, a fructofuranosidase, and its cross-reactive carbohydrate determinants were described by Foetisch and colleagues [36] as triggering molecules in tomato-sensitive subjects.

Pastorello and co-workers [37[•]] described previously identified 2S albumin (Jug r 1), vicillin (Jug r 2), and LTP (Jug r 3) from walnuts as allergens in walnut allergic patients without associated pollen allergy. As for other above reported allergenic sources local symptoms were frequently associated with asthma, urticaria, and anaphylaxis.

Although current knowledge on a rapidly evolving field of new allergenic sources and molecules is frequently and extensively reviewed [34[•],38^{••},39[•],40[•]], web-based databases can be useful for an up-to-date documentation on allergens. Table 1 reports some of the most interesting and complete available Internet databases.

Clinical aspects: diagnosis and epidemiology

Diagnosis of OAS seems to be much more important than in the past. Studies reported above clearly show that OAS should not be overlooked, and that OAS may be an important warning signal preceding more serious allergic symptoms. Therefore, a careful diagnostic work-up is indicated in patients reporting OAS to foods. This topic has been addressed in an interesting survey on definition and treatment of patients with OAS among clinical allergists carried out by Ma and colleagues [3]. Discrepancies in the approach to OAS as resulting from answers to a specific questionnaire may possibly be related to the term 'OAS', which is still not precisely defined, and due to the lack of diagnostic and therapeutic guidelines.

From a diagnostic point of view, several papers, either reviewing the topic of food allergy diagnosis [41] or addressing specific limitations of the current use of allergenic extracts for diagnosis [42,43], focused on the need of a component-based approach to food allergy diagnosis [44^{••}]. Several studies have demonstrated that, compared with extracts, a clearly higher sensitivity of detecting specific IgE *in vitro* can be obtained for foods known to cause OAS if purified allergen reagents are used. In the study by Mittag *et al.* [32^{••}] only 45% of 22 patients with pollen-related allergy to soybean had detectable IgE to the soy extract, whereas 96% were positive to the recombinant soy allergen rGly m 4. Similarly, higher IgE values were determined for Ara h 8 than for peanut extract in 13 of 20 patients, including two sera which were negative to

peanut extract [31^{••}]. Compared with hazelnut extract, the detection of the LTP Cor a 8 increased from 62 to 77% of 26 hazelnut allergic patients when rCor a 8 was used [24[•]]. The validity of this novel approach was also demonstrated by other allergenic molecule-based surveys [8,9,45,46]. For example, using commercially available recombinant Bet v 1 and Bet v 2 as a marker of sensitization to Bet v 1 and profilin-related food allergens, the authors were capable of identifying patients showing food allergy-related symptoms whether or not they had a current exposure to birch pollen [9]. The increasing use of allergenic molecules as markers of sensitization and the better definition of all the clinical aspects related to sensitization to an individual allergen may lead in the future to a detailed mapping of worldwide food allergy-related problems, including a more precise estimation of OAS prevalence.

Therapy: avoidance, drugs, and immunotherapy

The lack of agreement on the definition of OAS may influence not only the diagnostic but also the therapeutic approach to OAS [3].

Limitation of the exposure to identified offending foods should be established once the risk assessment has been carried out. On the basis of several recently reported studies [31^{••},32^{••},33], reactivity to allergenic molecules reported in the past as involved only in OAS should be carefully re-assessed because, in particular conditions, they can represent triggers of more severe allergic reactions. Another issue that should be addressed is about patients with mild OAS not willing to stop exposure to the allergenic food, and thus continuing to provoke symptoms. To date, there is no consensus established whether this should be strongly discouraged on the basis of a possible transition into a potentially severe generalized reaction or not. However, it should also be considered that patients' quality of life might be affected because of inadequate dietary restrictions.

Common anti-allergic drugs can be used by OAS affected patients when symptoms are local and mild, mainly to reduce the duration of manifestations. Masking mild OAS symptoms by antihistamines may consequently seduce patients to consume larger amounts of offending foods that are usually considered safe in small amounts and may thus lead to more severe symptoms. This may also be the case during the pollen season when patients treat their pollen-induced symptoms with antiallergic drugs.

To date, few studies have addressed the potential usefulness of specific subcutaneous immunotherapy (SCIT) for treatment of OAS. Controversial results have been reported by using allergenic extract-based SCIT. A first

study by Asero [47] reported successful treatment of apple-induced OAS in birch allergic patients. The study had limitations due to the use of self-reported symptoms as the only measure of OAS. More recently a study from the same author [48] examined in a prospective way the long lasting effect on SCIT on OAS. Fifty percent of patients who acquired a clinical tolerance to apple ingestion lost this tolerance in the 30-month period of follow-up observation. As for the former study, the lack of objective measurements in the enrolment and evaluation phases limits the value of these findings. No molecule-based approach was applied in either selection or treatment of patients.

The capacity of birch pollen extract SCIT to treat OAS induced by apple and hazelnut was evaluated in a study from Bucher and colleagues [49[•]]. As for Asero's study no objective measurement and no allergenic molecule approach was used except for the measurement of specific IgE and IgG before and after SCIT. On the basis of the obtained results the authors concluded that OAS is not an indication for SCIT with birch pollen extract. Asero commenting on Bucher's study [50[•]] believes that SCIT could be an efficacious treatment for OAS, but that higher dosage of relevant allergen extracts may be used for a successful treatment. To support this speculation, Bet v 1 concentrations of different commercial allergen products were reported. This discussion further strengthens the need for molecular approaches for improved characterization of patients' IgE reactivity as well as for allergen preparations. However, it does not seem realistic to try to reach such a conclusion on the basis of Bet v 1 content of the allergenic extracts without knowing the sensitization profile of the patients to birch allergens with known homologues in foods (e.g. Bet v 1, Bet v 2, Bet v 6, or Bet v 7).

An interesting therapeutic study was published by Bolhaar and co-workers [51^{••}]. The authors used DBPCFC before and after SCIT, measured skin test, specific IgE and IgG₄ reactivity to Bet v 1 and Mal d 1, and evaluated CD4⁺CD25⁺ Tregs variations. The SCIT trial was carried out using a birch pollen extract with a known content of Bet v 1. Thirteen patients were in the active treatment group, and 10 control participants received symptomatic medication. Reactivity in the food challenge and in the skin test decreased significantly for the actively treated group when compared with the symptomatic-treated control group. The treatment clearly induced an IgG₄ response to Bet v 1 and Mal d 1. However, no variations of CD4⁺CD25⁺ Tregs were recorded. The authors concluded that a potential beneficial effect on OAS of SCIT exists, although no placebo group was used for control purposes. The last published study on the use of specific immunotherapy in OAS is from Skamstrup Hansen and colleagues [52[•]].

These authors used both SCIT and SLIT treatment with a birch pollen extract, which was previously shown to successfully treat birch pollen-induced respiratory symptoms. Bet v 1 concentrations were known for both preparations. Hazelnut and apple were the OAS-inducing foods. Patients were recruited on the basis of self reported OAS, and monitored by means of open challenges. No molecular approach was used to monitor the patients' reactivity. No evidence of any positive effect of SCIT or SLIT on OAS was found. As for the other above reported studies some major limitations were present in the design of this study.

None of the studies reported above focused on the effect of birch pollen immunotherapy on allergies to other plant-derived foods containing Bet v 1-related food allergens such as carrot (Dau c 1), celery (Api g 1), or soybean (Gly m 4). If we accept the concept that the reactivity to foods is induced by the pollen allergen, an effect should be expected on all the related foods and the effect is expected to be strongly dependent on structural relationships and amino acid sequence identity between homologous molecules. Given that T cell reactivity of an allergen is important for the success of specific immunotherapy, the concept of co-treatment of OAS to plant derived foods with birch pollen is based on the assumption that complete cross-reactivity exists at the level of allergen-specific T cells. Studies on the major apple allergen, Mal d 1, and the major celery allergen, Api g 1, have indeed shown full T cell cross-reactivity to Bet v 1, and clearly stronger stimulation capacity of Bet v 1 compared to the food allergens [53,54]. Interestingly, an unpublished study in which one of the authors (S.V.) was involved revealed that both the major hazelnut allergen, Cor a 1.04, and the major carrot allergen, Dau c 1, contain T cell epitopes that lack cross-reactivity with Bet v 1 (Bohle *et al.* submitted). Thus, limited clinical efficacy of birch pollen specific immunotherapy on allergy to these foods may result, and it is recommended that allergy to these foods should be monitored during a birch-specific immunotherapy trial to answer this question.

Conclusion

A consensus on definition, diagnosis, prognosis, and therapy of OAS is needed to better define the features of this food-induced allergic disease. Efforts should be made to complete the classification of allergenic molecules capable of inducing OAS. Determination of threshold amounts of allergens inducing OAS and comparison to amounts eliciting subsequently more severe symptoms may help in establishing a risk assessment for the patient. The role of OAS as an alert symptom for more severe reactions should be considered, and interference of drugs used to treat concomitant respiratory diseases should be addressed.

SCIT or SLIT immunotherapy trials should have a more rigid design with respect to the patient enrolment phase, monitoring and choice of the extract for treatment. In addition to apple and hazelnut, the effect of specific immunotherapy on allergies to other pollen-related foods should be studied. Further studies on foods inducing OAS are required, preferably involving approaches based on purified allergen components or even epitopes. Study designs as strong as those used for specific immunotherapy trials for respiratory allergens should be used, and specific objective measurements including DBPCFC and placebo groups should always be included.

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